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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAROL, JODY LYNN	
ART UNIT	PAPER NUMBER
1627	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,050	PASTERNAK, GAVRIL W	
	Examiner	Art Unit	
	Jody L. Karol	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/3/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6,8,9 and 20-30* is/are pending in the application.

4a) Of the above claim(s) *26-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-6, 8-9, and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/3/2009 has been entered.

2. Receipt is acknowledged of applicant's Amendment/Remarks filed 8/3/2009. Claims 3-4, 8-9, and 24-25 have been amended. Claims 1-2, 7, and 10-19 have been cancelled. Claims 26-30 are newly added. Thus, claims 3-6, 8-9, and 20-30 are pending.

3. It is noted that in amended claim 24, the first "morphine" is newly added, but is not underlined as required by 37 CFR 1.21(c).

Election/Restrictions

4. Newly submitted claims 26-30 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims are

drawn to non-elected species of opioid analgesic (see 5/14/2008 Office Action confirming morphine was elected without traverse).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 26-30 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Claims 3-6, 8-9, and 20-25 are currently under consideration.

WITHDRAWN REJECTIONS

5. Upon further consideration, the rejection of claims 3-9 and 20-25 under 35 U.S.C. 103(a) as being obvious over Smith in view of Inturrisi et al. (US 6,00,258) is herein withdrawn in favor of the new ground(s) of rejection presented below.

Response to Arguments

6. Applicant's arguments filed 8/3/2009 have been fully considered but are moot in view of the new ground(s) of rejection presented below. However, Applicant's arguments are addressed in so much as they apply to the new ground(s) of rejection.

Applicant asserts that prior to the present invention, the common strategy of one of ordinary skill in the art of combination therapy, was to utilize two or more drugs of different mechanisms so as to reduce potential side effects. In response, it is respectfully submitted that regardless of the mechanism of action of the agents, it has been well established that it is obvious to combine individual compositions taught to

have the same utility to form a new composition for the very same purpose *In re Kerkhoven*, 626 F.2d 846, 205, U.S.P.Q. 1069 (C.C.P.A. 1980). Further, it is not guaranteed that an increase in side effects will be observed in combining two agents acting via the same mechanism.

The Applicants further argue that the data presented in Example 1 (see page 15 of the instant specification) to demonstrate the unexpected synergism between L-methadone and morphine (or other opioids) is commensurate with the scope of the claim. The Examiner respectfully disagrees. In the instant specification the data presented to demonstrate the synergistic effect of L-methadone and morphine is not commensurate with the scope of the claims because the synergistic effect is only demonstrated using specific dosages of L-methadone and morphine at specific ratios, whereas claim 1 is directed to any dosage of morphine and L-methadone at any ratio. For Example, in Example IV, the dose-response curves were generated using fixed ratios of L-methadone with morphine (or other opioids), using specific dosages, wherein the dosage of methadone ranges from 0.0 to 2 mg/kg while the dosage of morphine ranges from 0 to 5 mg/kg (see pages 17-18, Example IV and Figure 3). Synergistic effects are not demonstrated for dosages or ratio outside of the dosages/ratios in Figure 3. Further, in Example I, the interaction of L-methadone and the opioid is measured at a fixed dosage wherein the dosage is not indicated for all the drugs, including L-methadone (see page 16, lines 6-21). It is also noted that while the instant claims are directed to enantiomerically pure L-methadone or a mixture of DL-methadone having at least 65% L-methadone, the data provided in Table 1 and Figure 3 only demonstrates

the effect of a combination of L-methadone with the opioid analgesics. Data demonstrating a synergistic effect between morphine and a mixture of DL-methadone is not provided. Thus, it is unclear if the synergistic effect exhibited between morphine and L-methadone only occurs within the dosages/ratios exemplified, or if it occurs at any dosage or ratio as claimed. It is also unclear if a synergistic effect is still observed when mixtures of DL-methadone are utilized. Therefore, no clear and convincing unexpected results are seen to be present herein.

Thus, for these reasons, Applicant's arguments are found unpersuasive. The claims are considered to be properly rejected under 35 U.S.C. 103(a) as presented below.

NEW REJECTIONS

7. After further consideration, the following rejections have been newly added:

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 3-6, 8-9, and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahlström et al. ("Relation Between Morphine Pharmokinetics and Analgesia," *Journal of Pharmokinetics and Biopharmaceutics*, Vol. 6, No. 1, 1978, pgs 41-53) in view of Inturrisi (6,00,258).

The instant claims 3-9 and 20-23 are directed to methods of providing analgesia comprising administering a pharmaceutical composition(s) comprising enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone, and morphine, wherein the pharmaceutical composition(s) is/are administered in an amount and duration sufficient to potentiate an antinociceptive response. Claims 24-25 are directed to methods of potentiating an antinociceptive response comprising administering a pharmaceutical composition(s) comprising enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone, and morphine, wherein the pharmaceutical composition(s) is/are administered in an amount and duration sufficient to potentiate an antinociceptive response.

In regards to the recitation in claims 3-4 of "wherein the pharmaceutical composition(s) is/are administered in an amount and duration sufficient to potentiate an antinociceptive response," the amounts and duration sufficient to obtain this effect is not defined in the specification. Therefore, claims 3-4 and 22-25 (all containing similar

recitations) are broadly interpreted as administering any amount of L-methadone and morphine in any manner or duration.

Dahlström et al. teach administering morphine to male Sprague-Dawley rats at four different dosages (1.7, 2.5, 3.8, and 5.6 mg/kg) to elicit an analgesic effect (see pages 42-43). The analgesic effect is dose-dependent (see page 44, Figures 1-2).

Dahlström et al. do not teach administering enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone, or the dosage of L-methadone as claimed in the instant claims 5-6. Dahlström et al. do not explicitly teach the dosage of morphine in mg as claimed in the instant claims 8-9.

Inturrisi teaches in an exemplary test that L-methadone produces dose-dependent antinociception (analgesia) in rats with an ED_{50} value of 15.6 µg/rat, while D-methadone produced no antinociceptive effects at doses from 20 to 460 µg/rat (see column 3, lines 51-57). Inturrisi teaches that the D-isomer of methadone is 50-fold less potent analgesic in humans than L-methadone (see column 3, lines 27-33).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat analgesia by administering a combination of the morphine taught by Dahlström et al. and the L-isomer of methadone taught by Inturrisi. One of ordinary skill in the art would have been motivated to treat analgesia by combining morphine and L-methadone because both agents are taught in the prior art to have an analgesic effect. Further, one of ordinary skill in the art would have been motivated to use the L-isomer of methadone, or an increased amount of the L-isomer of methadone, in the method of treating analgesia because L-methadone is taught by Inturrisi to be the active isomer for

providing an analgesic effect, whereas the D-isomer is relatively inactive. One of ordinary skill in the art would have had a reasonable expectation of success in treating analgesia by combining the morphine taught by Dahlström et al. and the L-isomer of methadone taught by Inturrisi because both agents are taught by the prior art to provide an analgesic effect. It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose *In re Kerkhoven*, 626 F.2d 846, 205, U.S.P.Q. 1069 (C.C.P.A. 1980). Thus, combining the morphine taught by Dahlström et al. and the L-isomer of methadone taught by Inturrisi to provide a composition for providing an analgesic effect is obvious because both agents are taught by the prior art to provide an analgesic effect.

While the prior art references do not explicitly teach the dosage range of L-methadone or morphine in mg as claimed in the instant claims 5-6 and 8-9, the determination of an optimal dosage of L-methadone and morphine by routine experimentation is obvious absence a showing of criticality of the dosage. One have ordinary skill in the art would have been motivated to optimize the dosage of L-methadone and morphine in order to achieve the desired analgesic effects.

In regards to claims 24-25, the ability of compositions comprising enantiomerically pure L-methadone or a mixture of DL methadone having at least 65% L-methadone and morphine to potentiate an antinociceptive response is viewed as a mechanism of action. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise

known invention. *In re Wiseman*, 201 USPQ 658 (CCPA 1979). Since the method of providing analgesia obvious over Dahlström et al. in view of Inturrisi involves administering the same active agents to the same patient population at the same dosage, the method of providing analgesia will obviously potentiate an antinociceptive response.

Conclusion

No claims are allowed.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Jody L. Karol/

Examiner, Art Unit 1617

/Yong S. Chong/
Primary Examiner, Art Unit 1627